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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	31

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/194,356	NERI ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002 and 04 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-57* is/are pending in the application.

4a) Of the above claim(s) *48-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-37,43-45 and 53-57* is/are rejected.

7)☐ Claim(s) *38-42 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Claims 30-57 are pending.

Claims 1-29 have been cancelled.

Claims 48-52 are drawn to non-elected claims.

Claims 30-57 have been added.

Claims 38-42 have been amended.

Claims 30-47 and 53-57 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

3. The drawings continue to be objected to because of reasons cited on attached form PTO 948 completed by draftsman mailed August 14, 2001 with Paper number 13. Correction is required.

Withdrawn Objections

Claim Objections

4. Claims 5, 6 and 22 are no longer objected to because they have been cancelled.

5. The disclosure is no longer objected to because: (a) there is text on page 2, between lines 28-32.

Sequence Compliance

6. The application has been deemed to be in sequence compliance and the examination of the application has commenced.

Specification

7. The application now contains an abstract of the disclosure as required by 37 CFR 1.72(b). It was submitted with Amendment C as Paper number 17, received February 28, 2002.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

8. The rejection of claims 1-23, 27and 29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific binding members, single chain Fv molecules (CGS-1 and CGS-2), does not reasonably provide enablement for any specific binding member is withdrawn in light of Applicants' cancellation of the claims.

9. The rejection of claim 27 under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn in light of Applicants' cancellation of the claim.

10. The rejection of claims 6, 9-23, 27 and 29 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention is withdrawn in view of the cancellation of the claims.

11. The rejection of claims 6-23, 27 and 29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the cancellation of the claims.

Claim Rejections - 35 USC § 102

12. The rejection of claims 1-4, 6-9, 11-13, 19, 23, 27 and 29 under 35 U.S.C. 102(b) as being anticipated by European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS) is withdrawn in view of the cancellation of the claims.

Claim Rejections - 35 USC § 103

13. The rejection of claims 1, 6, 20 and 22 under 35 U.S.C. 103(a) as being unpatentable over European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS), in view of Bird et al. (Science 242:423-242, 1988) is withdrawn in view of the cancellation of the claims.

Maintained Objection

Specification

14. The disclosure is continues to be objected to because of the following informality: (a) there is no heading on page 20 referencing the brief description of the drawings.

Applicants are requested to list "Brief Description of the Drawings" before line 11 on the aforementioned page and review the following guidelines.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

New Grounds of Objection

Claim Objections

15. Claim 43 is objected to because of the following informality: it contains a grammatical error. After the recitation "claim 30" the recitation ", which" should follow. Correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

16. Claims 30-37, 43-45, 47 and 53-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific binding members, single chain Fv molecules (CGS-1 and CGS-2), does not reasonably provide enablement for any specific binding member. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue in anticipation of the instant rejection that "...it is not understood why any guidance...to a particular conformation itself is necessary for enablement. The routine methods for generating specific binding members such as antibodies and antibody fragments etc. rely on inherent capabilities of the methods to screen for successful matches. Precise knowledge of involved conformations is not needed." These arguments have been considered but found to be partially persuasive.

The Examiner concurs with the Applicants in regard to the ease at which one skilled in the art could screen for successful antibody and antibody fragment matches. Precise knowledge of involved conformations is not needed for such. However,

Applicants have broadly claimed specific binding members which could encompass a plethora of molecules such as collagen, hyaluronic acid and cell membranes. Applicants' claims do not exclude a number of molecules capable of binding directly to the ED-B oncofoetal domain of fibronectin. Applicants' disclosure sufficiently supports enablement for single chain Fv molecules, CGS-1 and CGS-2 and not enablement for *any* specific binding member. Accordingly, the rejection set forth in paragraph 12 of pages 4 and 5, Paper number 13, mailed August 13, 2001 is applicable to the instant claims in view that the scope of the previous claims are the same.

17. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 47 is drawn to the use of a specific binding member in an effective amount with the intended use being implementation in therapy. The specification while being enabling for a composition comprising scFV (CGS-1) and CGS-1, as well as control compositions and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition" comprising these same components. Claims drawn to "pharmaceutical compositions" are broadly interpreted to read on compositions effective for use as *in vivo* therapeutics. In the absence of an established role of these scFvs in diseases it is impossible to predict what if any therapeutic effect

the administration of these molecules would have for the treatment of cancers or in the broadly claimed "therapy". Applicants provide experimental data that suggest that scFv (CGS-1) is capable of targeting or localizing on a tumor (see page 38, lines 32-35 and Figure 5). However, there is no data or established precedent presented that would lead one of skill in the art to believe that the tumor was obliterated or that there was arrested tumor growth.

The selection and development of such therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of the scFvs as a therapeutic pharmacological agent and no such uses are art known. The specification does not suggests what type of tumors or cancers that the intended therapy would be able to treat. This reasonably conjures the question as to how selective the use of the claimed composition clearly is or would be. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the claimed pharmaceutical composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. There is no guidance as to how the instant molecules can be employed as therapeutic nor a basis to predict their efficacy in any therapy. Additionally, it would require undue experimentation of one skilled in the art to apply a method of treatment to a human based on the teachings of a method of treating a non-human animal. The applicant is advised to amend the claim to

delete the recitation of "pharmaceutical" and specify the type of therapy designated for the use of a composition.

18. Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The phrase "an effective amount" in claim 47 is indefinite when the claims fails to state the function that is to be achieve. In re Frederiksen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 30-37, 43, 47, 53 and 55-57 are rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS).

In anticipation of the instant rejection Applicants pointedly express disclosure in the specification that seemingly refutes the anticipatory reference, the European patent. Applicants also refer the Examiner's attention to several articles listed on the IDS. These points of view have been considered but found to be unpersuasive.

IDS reference BB, Carnemolla et al. (Int. J. Cancer 68: 397-405, 1996) states on page 397, column 2, first full paragraph that monoclonal antibody (mAb), BC-1 appears to recognize an epitope within the type III repeat 7. Claim 34 sets forth that the specific binding member of claim 30 binds to the recombinant FN containing type III homology repeats which include the ED-B domain. Accordingly, the BC-1 mAb still reads on the claims and the rejection set forth in Paper number 13, in paragraph 18 is instated for the instant claims.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 30-37, 43-45, 47, 53 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS), in view of Bird et al. (Science 242:423-242, 1988). Applicants have argued that the primary reference, European patent number 0 344 134 does not anticipate the instant claims. For the reasons discussed above this argument is not persuasive.

The teachings of patent 0 344 134, of a specific binding member that is the same as that claimed has been discussed in the paragraphs above. The aforementioned

reference does not teach that the antibody is single-chain Fv molecule (scFv) or a dimeric scFv.

However, Bird teaches the production of single-chain fragments, dimeric scFV and the efficacy of single-chain antibodies. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce single-chain antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in all references that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to penetrate the microcirculation surrounding solid tumors better.

23. Claims 30-37, 43, 47 and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS), in view of Clackson et al. (Nature 352:624-628, August 15, 1991). The teachings of patent 0 344 134, of a specific binding member that is the same as that claimed has been discussed in the 102(b) rejection. The aforementioned reference does not teach a specific binding member which is isolated from a synthetic molecular library.

However, Clackson teaches the production of single-chain fragments utilizing a random combinatorial library. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention by-passing hybridoma technology and animal immunization and using phage display creates produce single-chain antibodies, which

are high-affinity antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in all references that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to penetrate the microcirculation surrounding solid tumors better.

Allowable Subject Matter

24. Claims 38-42 and 46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

25. Claims 38-42 and 46 are free of the art.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
January 13, 2003